Spontaneous pregnancy in a woman with lupus and thyroiditis despite imminent premature ovarian failure

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We report a case of spontaneous pregnancy in a woman with lupus and clinical and hormonal changes suggesting imminent premature ovarian failure (POF).

CASE REPORT

A French woman born in 1962 had had Raynaud's phenomenon, photosensitivity, and subacute cutaneous lupus since the age of 15 years, which was treated with hydroxychloroquine. She underwent abortions for unwanted pregnancies in 1986, 1987, and 1988. Various progestin contraceptives were prescribed but rapidly stopped. In 1990 she presented with giant cell thyroiditis with normal thyroxine, thyroid stimulating hormone 6.1 mU/l (normal 0.1–3.2), and negative antithyroperoxidase and antithyroglobulin antibodies. L-Thyroxine 100 µg daily was started. In August 1992 endometriosis was discovered.

In February 1997 she complained of polyarthritis and sustained climacteric symptoms. She had regular menses with a short luteal phase. Her mother became menopausal at the age of 50. Follicle stimulating hormone (FSH) was increased (95 U/l) with normal oestradiol and karyotype. She was advised to become pregnant rapidly because of imminent POF. Antinuclear antibodies, anti-dsDNA, anti-extractable nuclear antigen and anticardiolipin were negative, total complement (CH_{50}) 34 U (normal 35–55), C3 0.66 g/l (normal 0.7–1.3), C4 0.1 g/l (normal 0.1–0.3). Antithyroglobulin became positive at 1000 U/ml (normal <100). Articular symptoms remitted with additional treatment with diclofenac.

In January 1998, FSH was 68 U/l and oestradiol 10 pg/ml, but cycles were still occasionally ovulatory. In the subsequent months, climacteric symptoms remitted. In October 1998 she became spontaneously pregnant. Pregnancy was uneventful with hydroxychloroquine and L-thyroxine. Caesarean section was indicated at 38 weeks because of abnormal cardiotocography, and she delivered a 2910 g healthy girl.

DISCUSSION

Our patient had an intermediate status between cutaneous and systemic lupus erythematosus. She developed imminent POF at the age of 35, without any other cause of ovarian failure. In particular, she did not take thalidomide.[1] Menopause is defined by the cessation of menstruation for ⩾12 months with low oestradiol and high gonadotrophins. Menopause is considered premature when it occurs at <40 years. POF is suggested in cases of amenorrhoea of ⩾4 months and confirmed by persistent FSH levels >40 U/l at least twice with a one month interval. Despite regular menses, our patient had clinical symptoms and hormonal changes suggesting imminent POF.

Premature menopause and POF affect 1–2% of women in the general population.[2] Although known causes of POF include X chromosome deletions, radiation, chemotherapy, and genetic defects of the gonadotrophin hormones or receptors, one third to one half of cases remain idiopathic. A significant proportion of patients with apparently idiopathic POF have evidence for an autoimmune aetiology because of positive autoantibodies.[3] However, confirmation of an autoimmune cause requires an ovarian biopsy. Anti-ovarian and other self tissue antibodies are present in up to one third of women with POF, but the tests are not well standardised and poorly correlated with ovarian histology. Autoimmune POF may occur as an isolated event, be part of the polyglandular autoimmune syndrome, or associated with other autoimmune diseases. Antibodies directed against the corpus luteum were found to be present in 22% of women with systemic lupus erythematosus (SLE) aged <40 years,[4] but they did not correlate with age, race, SLE activity, other autoantibodies, and treatment.[4]

Our patient had endometriosis, which is associated with an increased prevalence of various autoantibodies: antinuclear, anti-ribonucleoproteins, anti-smooth muscle, anticardiolipin, and lupus anticoagulant.[5] Endometriosis is characterised by abnormal aromatase activity in endometrial tissue, which leads to local production of oestrogen, inducing prostaglandin E_2 (PGE_2) formation. PGE_2 stimulates aromatase expression and establishes a positive feedback cycle. Endometriosis is associated with a twofold increased risk of SLE.[6] Oestradiol might cause autoimmune changes by mechanisms which have not been clearly elucidated. Association of endometriosis with POF[7] suggests that the primary mechanism is hormonal rather than immune.

POF is characterised by occasional recurrent ovarian activity, which occurs more often than in the natural menopause. Patients with POF still have a 5–10% chance of conceiving after diagnosis.[8] Glucocorticoids were tried without documented efficiency in autoimmune POF.[9] Women with hypergonadotrophic hypogonadism may become able to ovulate when treated with oestrogen alone or in combination with gonadotrophins, and may even conceive after treatment with gonadotrophin releasing hormone analogue and gonadotrophins.[10] In our patient, it is difficult to ascertain whether diclofenac and hydroxychloroquine favoured the spontaneous pregnancy because POF does not imply definitive sterility. About 80% of pregnancies after POF resulted in the birth of a healthy child. However, no treatment has been found which efficiently restores fertility in prospective controlled studies.

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Doppler ultrasound identifies increased resistive indices in SSc

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Cutaneous lesions in patients with systemic sclerosis (SSc) are characterised by fibrosis as well as by changes in the microvasculature. Various methods, including nailbed capillaroscopy, laser Doppler flow monitoring, thermography, and plethysmography, have been used to evaluate distal digital vascularisation and to assess the microvascular damage.[1–4] In studies using Doppler flowmetry and iontopheresis, patients with SSc showed reduced vasodilatory reserve of the skin microvasculature in response to ischaemia.[5 6] A new colour Doppler ultrasound (DU) technique of the nail bed appears to be able to detect and quantify early vascular damage in patients with connective tissue disease.[7] However, none of these methods has been generally introduced and accepted in clinical routine.

METHODS

This study aimed at assessing the digital blood flow of patients with SSc by DU. We compared the resistive indices (RIs) of 14 healthy subjects and 19 patients with SSc. Patients with SSc were classified as affected by limited SSc or diffuse SSc according to the criteria proposed by LeRoy *et al*.[8] The measurements were performed with an Ultramark 9 HDI duplex Doppler ultrasound (HDI; Advanced Technology Laboratories) after at least 15 minutes of thermal acclimatisation in our ultrasound laboratory. A 10 mHz probe was used for visualising digital vessels (Doppler filter 100 Hz, minimal flow velocity 10 cm/s). The outcome variable was the RI of the distal palmar arteries (arteriae digitales palmares propriae) of the thumb and the forefinger of the right and left hand (dig I and II). The arteries were identified by colour DU. The Doppler samples were obtained at the distal part of the digital artery, and the RI was determined by analysis of the spectral waveforms (fig 1). The RI was calculated according to the standard formula:

$$RI = (peak_{SV} - end_{DV})/peak_{SV}$$

where SV = systolic velocity; DV = diastolic velocity.

The RI of each of the digital arteries was determined in duplicate, and the mean of the resulting eight measurements was used for statistical analysis. Measurements were incomplete in seven patients with SSc, because it was impossible to identify all four digital arteries. In these seven patients we used the available measurements for statistical analysis. Statistical analysis was performed using the Mann-Whitney rank test.

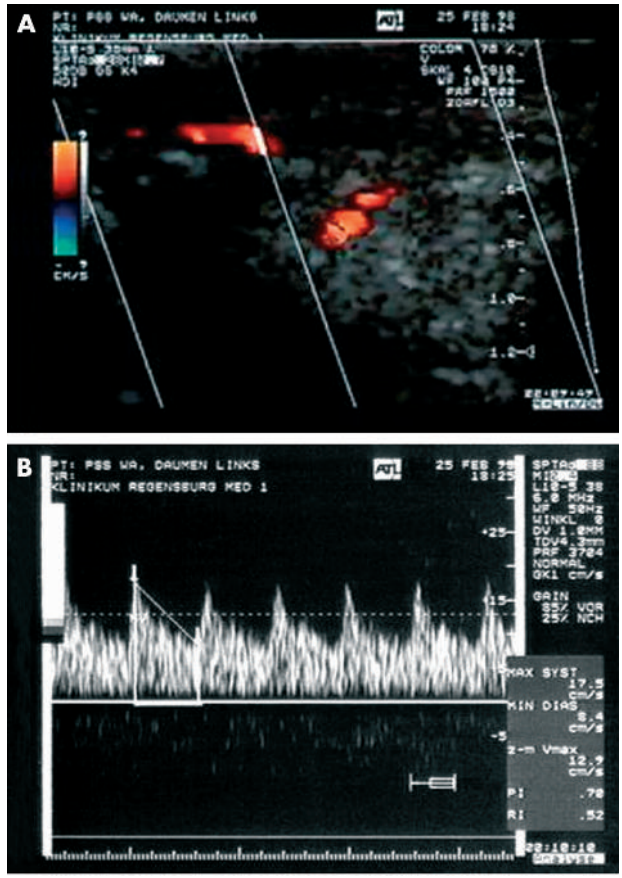

Figure 1 Picture of a colour Doppler ultrasound (A) and the associated spectral waveform (B) of the distal artery of the left thumb (patient with diffuse disease).

RESULTS

Table 1 shows the clinical characteristics of patients and controls. The mean of all measurements of all fingers showed a significantly higher RI for patients with SSc (limited and diffuse disease) (RI = 0.66) than for healthy controls (RI = 0.59; p = 0.01). However, there was a considerable overlap between the two groups. Individual digital analysis